

Errata and Addendum to the FDA Briefing Document

Pharmacy Compounding Advisory Committee

8-9 March 2016

FDA Errata to the Briefing Document

1. On page 8 of the Division of Anti-Infective Products' (DAIP) review, "[see Appendix 1]" should read "[see Appendix 2 attached to the Division of Bone, Reproductive and Urologic Products (DBRUP) review]"
2. On page 9 of DAIP's review, "[see Appendix 2]" should read "[see Appendix 3 of the DBRUP consult]"

FDA Addendum to the Briefing Document

1. Please see attached document that provides appendices for the Division of Bone, Reproductive and Urologic Products' (DBRUP) review of quinacrine.

# Appendix 1

# FDA TALK PAPER

*Food and Drug Administration  
U.S. Department of Health and Human Services  
Public Health Service 5600 Fishers Lane Rockville, MD 20857*

FDA Talk Papers are prepared by the Press Office to guide FDA personnel in responding with consistency and accuracy to questions from the public on subjects of current interest. Talk Papers are subject to change as more information becomes available.

T97-26

June 17, 1997

Brad Stone: (301) 443-3285

Broadcast Media: (301) 827-3434

Consumer Hotline/Laura Alvey: (800)

## FDA Warns Consumers on Dangerous Products Promoted on the Internet

FDA is warning consumers not to purchase certain unapproved products that pose significant, possibly life-threatening health risks. The products in question, which are offered for sale on the Internet, are home abortion kits and female self-sterilization kits.

The abortion kit inaccurately touts itself as a "complete kit for early pregnancy termination without surgery...scientifically proved safe and unrisky." The kit provides a combination of drugs that are not approved by FDA to terminate pregnancy. The agency conducted a health hazard assessment of this product and concluded that using the kit without a physician's supervision could cause heavy vaginal bleeding and even death. Birth defects also can result if a pregnancy is carried to term after taking these drugs.

The self sterilization kit claims to use a method similar to inserting an IUD and to have a much lower risk than that associated with surgical sterilization. The kit uses pellets of **quinacrine hydrochloride**, an unapproved drug, which can cause ectopic pregnancy, abnormal pregnancies, and permanent damage to a woman's reproductive organs.

FDA urges consumers not to purchase or use these or similar products promoted via Internet or any other media. The Federal Food, Drug, and Cosmetic Act prohibits the sale and promotion of unapproved medical products. The agency is continuing to investigate and monitor these products.

Consumers who have suffered an adverse event as a result of using these "kits" and health professionals who have treated such patients are asked to report the event to the agency's Medwatch adverse event and product problem hot line at 1-800-FDA-1088.

####

**FDA HOME PAGE**

<http://www.fda.gov/search97cgi/s97is.dll?action=View&VdkVpwKey=http%3A%2F%2F626982111>



# Appendix 2

Controlled Correspondence Response

Log Number: DRUDP 137

Date: August 26, 1998

To: Lisa Rarick, MD *M. Mann for L. Rarick.*  
Division Director  
DRUDP

From: Susan Allen, MD, MPH  
Medical Officer  
DRUDP

Subject matter: Health Hazard Evaluation Summary of a kit for intrauterine insertion of Quinacrine Hydrochloride pellets for female sterilization.

**I. Background and Regulatory History:**

Quinacrine Hydrochloride (QH) tablets were originally marketed in the United States in the early 1930s for the treatment of malaria. The drug was used extensively during World War II for this indication and was typically administered in a dose of 100-200 mg per day taken orally. In 1964, an injectable form of Quinacrine was approved for the treatment of recurrent ascites associated with several types of cancer. Marketing of both of these quinacrine products was subsequently discontinued (in July of 1994 for the oral tablets and in January of 1977 for the injectable formulation). Thus, there are no formulations of QH currently marketed in the United States.

Quinacrine was first studied in Chile as a possible agent for non-surgical female sterilization in the 1960s and early 1970s by Jaime Zipper. Following intrauterine administration, QH acts as a sclerosing agent, causing a chemical reaction within the uterus and fallopian tubes that results in significant tissue damage and scarring of tissue exposed to the drug. Initial studies of QH for the indication of female sterilization involved intrauterine administration of QH as a slurry formulation. At least 3 deaths have been reported following intrauterine administration of the slurry formulation. Although two of the women who died received concurrent administration of lidocaine, the contributory role this anesthetic played in their deaths is unknown. Because of these deaths, a pellet formulation of quinacrine was developed for intrauterine insertion.

Researchers and clinicians in several countries have conducted studies on the administration of QH pellets for non-surgical female sterilization. Since 1977, over 100,000 women in 20 countries (primarily in the developing world) have received intrauterine insertions of QH for the purpose of non-surgical sterilization. In 1981, an IND for QH pellets was granted by the FDA to \_\_\_\_\_, and three studies were initiated under this IND. Two of the three studies were subsequently stopped due to slow recruitment, and the IND was canceled in 1990 because of several factors including concerns about the drug's mutagenicity, long-term safety and possible carcinogenicity.

**II. Quinacrine Sterilization—The Procedure**

The process of Quinacrine Sterilization (QS) involves transcervical delivery of 7 pellets, each containing 36 mg of QH, for a total dose of 252 mg. The pellets are preloaded into a modified IUD inserter which is introduced into the uterine cavity and directed toward the fundus. The pellets are dispensed and slowly



liquify, causing local tissue damage to both the endometrium and the fallopian tubes. Subsequent scar formation results in tubal occlusion.

The dosing regimen for QS has yet to be standardized, with single and multiple doses (each one month apart) of 7 or more pellets having been studied. Wide variations in efficacy rates with the procedure have been noted depending on the dosing regimen used, the age of the woman undergoing the procedure, use of concurrent adjuvant therapies and the skill of the clinician performing the procedure. Cumulative pregnancy rates have been noted to be higher in women less than 35 years of age (failure rates as high as 10 per 100 woman-years of use when compared to women over 35 years of age in whom cumulative failure rates were 3 per 100 woman-years of use), with regimens involving fewer insertions, with regimens not accompanied by supplemental contraception 3 months post-initial insertion and with less clinician skill.

Currently available information on the safety, efficacy and clinical experience with QS is based upon clinical trials which lack appropriate study design, are poorly controlled, have incomplete follow-up on study participants and are not comparable due to differences in formulation, dose, dosing regimen and adjuvant therapies used. These trials have employed a variety of formulations, doses (180 mg, 252 mg, 288 mg, 324 mg) and dosing regimens (single versus multiple insertions) of QH pellets and have included the use of various adjuvant therapies, such as Depo-Provera, non-steroidal anti-inflammatory drugs (NSAIDs), copper and betamethasone. While published studies report no deaths immediately following the insertion of QH pellets, the studies conducted to date do not provide convincing evidence of this product's safety.

### III. Safety Assessment and Health Hazard Evaluation

Available toxicological, pharmacokinetic and pharmacodynamic data from human studies of QH come primarily from its use as an orally administered antimalarial therapy used extensively during the 1940s and 1950s. Human data derived from those studies are inadequate for the purpose of assessing the safety of Quinacrine as an intrauterine sterilizing agent due to the fact that direct application of QH pellets to the endometrium will result in local concentrations of the drug that are considerably higher than those attained as a result of oral administration of the tablet formulation.

Safety concerns with QH pellets for intrauterine administration are based on (1) results from previously conducted toxicology studies on the oral formulation and (2) the lack of adequate toxicology testing on the intrauterine pellet formulation.

#### A. Safety issues related to previously conducted toxicology studies on QH

There is a lack of relevant and high quality toxicological data on which to base a complete safety assessment of QS. Available data are deficient and raise concerns in 3 areas:

##### 1) Possible carcinogenicity of QH:

Quinacrine is a known mutagen and has tested positive in several genotoxicity tests. Positive results in the mutagenicity battery correlate highly with positive results in rodent carcinogenicity studies. Compounds having this profile are thus worrisome from the point of view of risk of cancer development in humans.

Because intrauterine administration of QH pellets will result in significant tissue damage (by virtue of its mechanism of action) in the presence of a known mutagen, serious concerns exist that such exposure could result in development of cancer of the reproductive tract. A retrospective study of 421 Chilean women who had undergone QS between 1977 and 1982 revealed a cluster of nine cases of cancer.

A second retrospective cohort study was conducted in 1,492 Chilean women (802 of whom were personally interviewed and 690 of whom were not personally interviewed, but had their clinic charts reviewed) who had undergone QS between 1977 and 1989. A total of 17 cases of invasive cancer of various organ systems were found. This total number of observed cases of invasive cancer was higher than the expected number (11.8), and included higher than expected numbers of cases of specific types of cancer (breast and cervix) for that population. The cases reported also included a single case of leiomyosarcoma (a rare, but usually fatal, uterine tumor). With regard to the potential effect of QH on the occurrence of cervical cancer, it is not known whether or in what way quinacrine interacts with Human Papilloma Virus (HPV), one of the primary risk factors for cervical cancer. Reported human experience to date with QS is not sufficient to demonstrate the safety of the procedure with regard to carcinogenicity.

2) Lack of sufficient pharmacokinetic data:

Pharmacokinetic studies conducted in humans following oral administration of QH have shown that the drug has high tissue and plasma binding affinity. QH has a relatively long half-life (7 days) in humans and certain animal species (dogs). Only one completed U.S. study with a sample size of 10 provided pharmacokinetic data following intrauterine administration of QH pellets. This study showed that 24 hours following intrauterine administration of QH pellets, reproductive tissue levels of QH were higher than plasma levels of the drug. There is insufficient data available to assess tissue half-life of QH following intrauterine administration and to correlate plasma drug levels with reproductive tissue drug levels beyond 24 hours post-pellet administration. Because of QH's long half-life and slow excretion following oral administration, concerns exist related to possible continuous exposure (as long as weeks at a time) of the endometrium to the drug following intrauterine insertion.

3) Concerns related to pharmacodynamic issues:

The endometrium is a highly proliferative site at which spontaneous neoplasia occurs in approximately 1% of the US population of women. Intrauterine instillation of cytotoxic agents has been noted to be unsuccessful for complete destruction of the endometrium and has resulted in neoplastic transformation of residual endometrial cells. Drugs such as quinacrine with positive mutagenicity and cytotoxicity profiles are of concern with regard to increased cancer risks in humans.

B. Clinical Safety Concerns related to QS

Clinically, safety concerns with QS fall into two categories: (1) short-term risks and (2) long-term risks.

Short-term safety risks with QS include:


1. Uterine perforation during insertion (*reported incidence < 1%*)
2. Possible intraperitoneal exposure following uterine perforation, with subsequent formation of adhesions (*incidence unknown*)
3. Possible intraperitoneal leakage of dissolved drug product (*incidence unknown*)
4. Cervical and vaginal exposure and effects (*studies have shown an average leakage of 27% of drug from uterine cavity into vagina*)
5. Severe uterine bleeding post-administration (*reported incidence < 1%*)
6. Formation of hematomata
7. Drug-drug interactions
8. CNS excitation
9. Exacerbation of porphyria
10. Exacerbation of psoriasis
11. Generalized allergic reaction (*reported incidence 1/30,000*)

**Long-term safety risks with QS:**

The basis for most of the long-term safety concerns with this product are due to its known mutagenicity and probable carcinogenicity. They include:

1. Possible increased risk for reproductive tract cancers
2. Development of abnormal uterine lesions (*such as synechia*)
3. Procedure failure (*wide variation in efficacy rates*)
4. Ectopic pregnancy
5. Prolonged amenorrhea (*10% occurrence one year post-administration*)
6. Fetal exposure (*Risks unknown but of concern since QH crosses the placenta. One case of an anencephalic infant conceived 2.5 months following intrauterine insertion of QH was reported in Vietnam. In addition, one case of possible renal agenesis and hydrocephalus in an infant born to a woman taking an unknown formulation QH was reported.*)

In summary, although Quinacrine has been used systemically for the treatment of malaria for decades, the risks of administration of the drug in healthy, young women are markedly different from those associated with treatment of an infectious (and potentially life-threatening) disease. For the proposed indication of non-surgical female sterilization, QH is not being used to treat a disease condition; therefore, the potential and known risks listed above may outweigh any proposed advantages this procedure may have over surgical sterilization in the U.S. The true safety profile of this product for U.S. women may be determined only when appropriately designed, well-controlled and adequately conducted clinical trials are performed under an IND, as previously conveyed to the sponsor.



Susan S. Allen, MD, MPH  
Medical Officer



## Office of Compliance/CDER Health Hazard Evaluation Criteria for Human Drug Recalls

It should be noted that Quinacrine Hydrochloride pellets for the indication of non-surgical female sterilization have not been approved for use in the U.S. This drug product is not being considered for "recall" since it has never been approved for use in this country. Therefore, the responses listed below are given in terms of a risk assessment of product use in the U.S.

**Product:** Quinacrine Hydrochloride pellets for intrauterine insertion

**Firm:**

### Questions:

#### **1. Any disease, injuries or adverse reactions that could occur from the use of the product:**

These conditions are described in detail in Section III of the Health Hazard Evaluation Summary above and include:

##### **Short-term safety risks:**

1. Uterine perforation during insertion
2. Possible intraperitoneal administration following uterine perforation
3. Possible intraperitoneal leakage of dissolved drug product from the fallopian tubes
4. Cervical and vaginal exposure and effects
5. Severe uterine bleeding post-administration
6. Formation of hematomata
7. Drug-drug interactions
8. CNS excitation
9. Exacerbation of porphyria
10. Exacerbation of psoriasis
11. Generalized allergic reaction

##### **Long-term safety risks:**

The basis for most of the long-term safety concerns with this product are due to its known mutagenicity and probable carcinogenicity. They include:

1. Possible increased risk for reproductive tract cancers
2. Development of abnormal uterine lesions
3. Procedure failure
4. Ectopic pregnancy
5. Prolonged amenorrhea
6. Fetal exposure

#### **2. Existing conditions that could contribute to a clinical situation that would expose humans to a health hazard by use of the product:**

- a. Pregnancy
- b. Cervical or vaginal infection
- c. Uterine or fallopian tube infection
- d. Cervical HPV infection or dysplasia
- e. Previous ectopic pregnancy
- f. History of, or current, dermatitis (especially psoriasis)
- g. History of severe mental conditions (including psychosis or epilepsy)

- h. Uterine anomalies (including fibroids)
- i. Porphyria

**3. Assessment of hazard to various segments of the population, including evaluation of the likelihood of exposure of these groups to the product:**

The primary segments of the population that could be adversely affected by intrauterine administration of QH include women as a group, pregnant women, the developing fetus, women with certain medical conditions, women having recently undergone gynecologic surgery.

The risks to women as a group are described in detail in sections III A and III B of the Health Hazard Evaluation Summary above and include both short-term and long-term risks. Because adequate preclinical testing (including toxicology, pharmacokinetics, pharmacodynamics and carcinogenicity testing) has not been performed for the intrauterine pellet formulation of this product, the extent of these risks for women cannot yet be fully assessed. However, the greatest concern from a clinical perspective is related to the known mutagenicity and probable carcinogenicity of this drug. As described in Section IIIB above, several cases of invasive cancer have been noted in Chilean women who underwent previous QS.

As noted above, QH crosses the placenta. Therefore, its inadvertent use in a pregnant woman could pose health risks to a developing fetus. Two cases of fetal anomaly have been noted following QH exposure: One case of anencephaly (a fatal condition involving absence of formation of the brain) in a woman who underwent QS and one case of possible renal agenesis and hydrocephalus in an infant born to a woman receiving QH in an unknown formulation. Once again, because adequate preclinical testing has not been performed for the intrauterine pellet formulation of this product, the extent of fetal risk cannot yet be fully assessed.

QH is excreted in breast milk. The effects excretion of QH in breast milk could have on a lactating infant is not known, although no adverse effects have been reported.

Women with medical conditions including epilepsy and porphyria, skin conditions such as psoriasis, and reproductive tract abnormalities such as leiomyomas (uterine fibroids) could be exposed to a health hazard by use of QH for non-surgical sterilization. The prevalence of these conditions in US women is as follows:

1. Epilepsy: 1% of the US population of women (*approximately 1.1 million women*)
2. Porphyria: < 1% of the US population of women
3. Psoriasis: 1% of the US population of women
4. Uterine Leiomyomata: 20-30% of women over the age of 30 years
5. Cervical HPV infection: 10-25% of the US population of women

A woman who has any of the above conditions and desires sterilization could have a significant likelihood of exposure to intrauterine QH pellets if the product were being made available by her health care provider. According to a press statement made by \_\_\_\_\_ which appeared in the July 21, 1998 edition of *The News and Observer* (Raleigh, NC), "steps are being taken to make QS available...in North Carolina." The extent of his efforts in this regard is unknown.

Women with uterine abnormalities (particularly uterine fibroids) could be at increased risk for uterine bleeding secondary to trauma following attempted insertion of the pellets into a uterine cavity which is distorted by the fibroid. In addition, if the presence of the fibroid distorts the uterine cavity, the likelihood of correct placement of the pellets is reduced. Non-fundal placement of the pellets is associated with increased vaginal leakage of dissolved pellets into the vagina, leading to increased vaginal and cervical exposure to the drug.

Women with cervical abnormalities could also be at increased risk for development of more severe lesions following QH exposure. As stated in the summary above, a 1995 study found a higher than expected rate

of invasive cervical cancer in 1,492 Chilean women who had undergone previous QS. The role of HPV as an etiologic agent in cervical cancer is well established. It is unknown whether or in what way QH interacts with HPV and, hence, might increase a woman's risk of developing cervical cancer; however, the relatively high prevalence of cervical HPV infection in US women (10-25% infected) could correlate with a significant absolute number of women at risk for developing more severe cervical lesions following QH exposure.

**4. Assessment of the degree of seriousness of the health hazard to which the population would be exposed:**

- (a) Life-threatening: From published literature, it appears that the risk of death following QH pellet administration into the uterine cavity is low.
- (b) Severe: The possibility of increased risk of permanent significant disability following intrauterine administration of QH pellets does exist, with the greatest concern being that of carcinogenesis. As noted above, QH is a known mutagen and probable carcinogen. Retrospective studies in Chilean women who had undergone QS revealed a higher than expected incidence of invasive cervical and breast cancer, in addition to a single reported case of uterine leiomyosarcoma. Formation of uterine synechia, severe bleeding (which may require hysterectomy), and formation of pelvic adhesions following inadvertent intraperitoneal administration of QH represent other possible severe health hazards that could occur following QS. The degree of risk for these types of health hazards can only be assessed through adequate preclinical and clinical testing, accompanied by long-term follow-up of women exposed to the product.
- (c) Moderate: Uterine perforation during the QS procedure, possible intraperitoneal drug administration following perforation, severe uterine bleeding not requiring hysterectomy, formation of hematometra following the procedure, and ectopic pregnancy represent possible health hazards of moderate seriousness associated with QS.
- (d) Limited: Vaginal and vulvar exposure to leakage of dissolved QH pellets, transient CNS excitation, and prolonged amenorrhea represent health hazards of limited seriousness associated with QS.

**5. Likelihood of occurrence of the hazard:**

As detailed in the response to question # 3 above, the likelihood of occurrence of each of the health hazards described depends upon the prevalence of the clinical condition as well as the availability of the product. The incidence of each clinical condition that could result in a significant health hazard is provided in answer #3. The degree to which QS is or will be made available in the US is unknown at the present time; however, the intention to increase the availability of the product for US women has been clearly stated by representatives of

**6. Immediate or long-range consequences:**

- a. Immediate consequences: Immediate consequences following intrauterine exposure to QH pellets are listed as "short-term safety risks" in Section IIIB of the Health Hazard Evaluation Summary above. They include:
  - 1. Uterine perforation during insertion
  - 2. Possible intraperitoneal administration following uterine perforation
  - 3. Possible intraperitoneal leakage of dissolved drug product from the fallopian tubes
  - 4. Cervical and vaginal exposure and effects
  - 5. Severe uterine bleeding post-administration
  - 6. Formation of hematometra
  - 7. Drug-drug interactions
  - 8. CNS excitation

9. Exacerbation of porphyria
10. Exacerbation of psoriasis
11. Generalized allergic reaction

b. **Long-range consequences:** Long-range consequences following intrauterine exposure to QP are listed as "long-term safety risk" in Section IIIB of the Health Hazard Evaluation Summary above. They include:

1. Possible increased risk for reproductive tract cancers
2. Development of abnormal uterine lesions
3. Procedure failure
4. Ectopic pregnancy
5. Prolonged amenorrhea
6. Fetal exposure

7. **Other pertinent factors if applicable:**

During a meeting held between DRUDP and representatives of \_\_\_\_\_ on May 8, 1998, DRUDP informed \_\_\_\_\_ that QS using reformulated QH pellets did not constitute off-label use of an approved drug product as described in 21 CFR 312.2(b). They were told that QH pellets for the indication of non-surgical sterilization could only be administered in the US under an IND. In addition, they were informed of preclinical testing requirements for continued development of the product in the US.

8. **Recall classification based on the health hazard evaluation:**

As noted in the response to question # 4 above, most of the possible health hazards which could result following intrauterine administration of QH pellets fall into the categories of "severe" and "moderate". For those possible health hazards classified as "severe", the recall classification would be that of Class I. For those possible health hazards classified as "moderate", the recall classification would be that of Class II.

Prepared by: Susan S. Allen, MD Date: 8/26/98  
 Susan S. Allen, MD, MPH  
 Medical Officer, DRUDP

Concurrence: Marianne Mann, MD Date: 8/26/98  
 Marianne Mann, MD  
 Deputy Director, DRUDP

McMann (for L. Rarick) Date: 8/26/98  
 Lisa Rarick, MD  
 Division Director, DRUDP

James M. Bilstad Date: 8/26/98  
 James M. Bilstad, MD  
 Director, ODE II

# Appendix 3





OCT 14 1998

## WARNING LETTER

Elton Kessel, M.D., .P.H.D.  
Secretary General  
International Federation for Family Health  
6100 NE Mineral Springs Road  
Carlton, Oregon 97111

Re: 99-HFD-312-02

Dear Dr. Kessel:

This letter is in reference to the importation, processing, marketing, and possible exportation of quinacrine pellets and quinacrine inserters (each inserter contains seven quinacrine pellets). Labeling with your product states that the quinacrine is intended for "NONSURGICAL FEMALE STERILIZATION."

The Food and Drug Administration (FDA) has concluded that quinacrine pellets for non-surgical female sterilization is an unapproved new drug and a misbranded drug in violation of the Federal Food, Drug, and Cosmetic Act (Act), and an unsafe use of this drug product. The FDA is very concerned about the safety risks associated with the use of this drug for non-surgical female sterilization, and its effects on women and the fetus if a woman is, or becomes pregnant. This safety concern is shared by the World Health Organization (WHO), which has issued statements that quinacrine for non-surgical female sterilization should not occur until completion of toxicology, genotoxicity and possibly carcinogenicity testing. Reportedly, several countries including India and Chile, have banned this method of non-surgical sterilization. We are not aware of any country that has approved this product for non-surgical female sterilization.

Toxicology, genotoxicity, and carcinogenicity studies are normally part of appropriately designed, well controlled, clinical trials conducted under an Investigational New Drug Application (IND) filed with the FDA. The Agency's safety



concerns and IND requirements prior to marketing of this drug for non-surgical female sterilization were previously conveyed to you during your May 8, 1998 meeting with the FDA's Center for Drug Evaluation and Research (CDER) Division of Reproductive and Urologic Drug Products.

The possible safety risks associated with this drug's use include but are not limited to:

- possible increased risk for reproductive tract cancers
- development of abnormal uterine lesions
- ectopic pregnancy
- prolonged amenorrhea
- procedure failure (variable efficacy rates)
- fetal exposure

The FDA has reviewed your firm's product labeling, training materials, videos, instruction manuals, patient pamphlets, and Internet site for this product which demonstrate that your product is intended "to affect the structure or any function of the body," as described in section 201(g) of the Act. Consequently, your product, quinacrine pellets for non-surgical sterilization, is a drug.

The FDA is unaware of any scientific evidence from adequate and well-controlled studies that this drug is generally recognized as safe and effective for this intended use. Accordingly, this product is a "new drug" under section 201(p) of the Act and may not be marketed in the United States because it is not the subject of an approved application as described in section 505(b) of the Act.

Further, this drug is misbranded pursuant to section 502(f)(1) of the Act in that its labeling fails to bear adequate directions for the uses for which it is being offered.

Because this product is an unapproved new drug and misbranded under the Act, import of the product into the United States is prohibited by section 301(a), (d) of the Act.

In addition, based on the information available to FDA, the Act prohibits the export of this product from the United States to a foreign country. Although section 802 of the Act permits the export of certain unapproved new drugs from the United States, this product does not appear to comply with the requirements of that section. The principal provision authorizing the exportation of unapproved new drugs is section 802(b)(1)(A) of the Act, and provides that a drug "may be exported to any



country, if the drug...complies with the laws of that country and has valid marketing authorization by the appropriate authority" in Australia, Canada, Israel, New Zealand, Switzerland, South Africa, or any member nation in the European Union on the European Economic Area." A drug product exported pursuant to section 802 must meet several other requirements, including not being in conflict with the laws of the country to which it is to be exported (section 802(f)(3)), and not presenting an imminent hazard to the public health of the country to which it is to be exported (section 802(f)(4)). The information available to the FDA, however, indicates that the product at issue does not meet even the threshold requirement for export in that it is not approved for use in non-surgical female sterilization in any country listed in section 802(b)(1)(A). Export of this drug product, therefore, would violate the Act.

The violations described above do not necessarily constitute an exhaustive list. It is your responsibility to ensure that the drug products you distribute meet all the requirements of the Act and its implementing regulations. We request that you take prompt action to correct these violations and report to us within 15 days any and all actions you intend to take for correction as well as any actions to prevent any further violation. Failure to promptly correct these violations may result in regulatory action without further notice. Such actions may include seizure, injunction, and/or criminal prosecution.

Dr. Stephen D. Mumford stated to us that the United States Pharmacopeia (U.S.P.) Convention has taken the position that quinacrine for sterilization has been sufficiently tested and its safety and efficacy adequately demonstrated, and listed this method as an accepted use of this drug for American women. The U.S.P. is a standard-setting organization in the areas of strength, quality, purity, and method of analysis. The fact that an ingredient is listed in any of the U.S.P. publications, including the U.S.P. DI does not mean that your product or another product is necessarily recognized as safe and effective for its intended uses. Further, the U.S.P. DI documents are not "full disclosure" documents that include all the information required by law and regulation.

On September 30, 1998 an investigator from our Seattle District office met with you at your Carlton, Oregon address, and he asked you to identify the location of the remaining product inventory reportedly consisting of approximately 290,000 quinacrine pellets and 1536 quinacrine filled inserters. At that time and thus far, you have chosen not to provide us with the location of the quinacrine products. The FDA is concerned about the health of

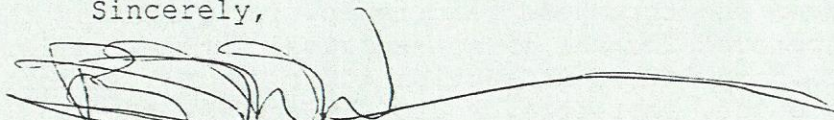


Page 4 - Dr. Elton Kessel

women and children in the United States and other countries, and that this product may be exported to another country or distributed for use in the United States. We request that you immediately halt all distribution of any and all quinacrine under your control, identify its location, and voluntarily destroy it under FDA supervision.

Your reply to this letter should be addressed to William G. Nychis, Compliance Officer, U.S. Food & Drug Administration, OTC Compliance Team (HFD-312), at the address noted above. You may contact him directly by telephone (301-827-7362) if necessary.

Sincerely,

A handwritten signature in dark ink, appearing to read 'Bradford W. Williams', with a long horizontal flourish extending to the right.

Bradford W. Williams  
Director  
Division of Labeling and  
Nonprescription Drug Compliance  
Center for Drug Evaluation and Research

# Appendix 4



OCT 14 1998

**WARNING LETTER**

The Center for Research on Population & Security  
322 Azalea Drive  
Chapel Hill, NC 27514

Re: 99-HFD-312-01

Dear Dr.

This letter is in reference to the importation, processing, marketing, and possible exportation of quinacrine pellets and quinacrine inserters (each inserter contains seven quinacrine pellets). Labeling with your product states that the quinacrine is intended for "NONSURGICAL FEMALE STERILIZATION."

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Toxicology, genotoxicity, and carcinogenicity studies are normally part of appropriately designed, well controlled, clinical trials conducted under an Investigational New Drug

Application (IND) filed with the FDA. The Agency's safety concerns and IND requirements prior to marketing of this drug for non-surgical female sterilization were previously conveyed to you during your May 8, 1998 meeting with the FDA's Center for Drug Evaluation and Research (CDER) Division of Reproductive and Urologic Drug Products.

The possible safety risks associated with this drug's use include but are not limited to:

- possible increased risk for reproductive tract cancers
- development of abnormal uterine lesions
- ectopic pregnancy
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The FDA has reviewed your firm's product labeling, training materials, videos, instruction manuals, patient pamphlets, and Internet site for this product which demonstrate that your product is intended "to affect the structure or any function of the body," as described in section 201(g) of the Act. Consequently, your product, quinacrine pellets for non-surgical sterilization, is a drug.

The FDA is unaware of any scientific evidence from adequate and well-controlled studies that this drug is generally recognized as safe and effective for this intended use. Accordingly, this product is a "new drug" under section 201(p) of the Act and may not be marketed in the United States because it is not the subject of an approved application as described in section 505(b) of the Act.

Further, this drug is misbranded pursuant to section 502(f)(1) of the Act in that its labeling fails to bear adequate directions for the uses for which it is being offered.

Because this product is an unapproved new drug and misbranded under the Act, import of the product into the United States is prohibited by section 301(a), (d) of the Act.

In addition, based on the information available to FDA, the Act prohibits the export of this product from the United States to a foreign country. Although section 802 of the Act permits the export of certain unapproved new drugs from the United States, this product does not appear to comply with the requirements of that section. The principal provision authorizing the exportation of unapproved new drugs is section 802(b)(1)(A) of



the Act, and provides that a drug "may be exported to any country, if the drug...complies with the laws of that country and has valid marketing authorization by the appropriate authority" in Australia, Canada, Israel, New Zealand, Switzerland, South Africa, or any member nation in the European Union on the European Economic Area." A drug product exported pursuant to section 802 must meet several other requirements, including not being in conflict with the laws of the country to which it is to be exported (section 802(f)(3)), and not presenting an imminent hazard to the public health of the country to which it is to be exported (section 802(f)(4)). The information available to the FDA, however, indicates that the product at issue does not meet even the threshold requirement for export in that it is not approved for use in non-surgical female sterilization in any country listed in section 802(b)(1)(A). Export of this drug product, therefore, would violate the Act.

The violations described above do not necessarily constitute an exhaustive list. It is your responsibility to ensure that the drug products you distribute meet all the requirements of the Act and its implementing regulations. We request that you take prompt action to correct these violations and report to us within 15 days any and all actions you intend to take for correction as well as any actions to prevent any further violation. Failure to promptly correct these violations may result in regulatory action without further notice. Such actions may include seizure, injunction, and/or criminal prosecution.

You stated to us that the United States Pharmacopeia (U.S.P.) Convention has taken the position that quinacrine for sterilization has been sufficiently tested and its safety and efficacy adequately demonstrated, and listed this method as an accepted use of this drug for American women. The U.S.P. is a standard-setting organization in the areas of strength, quality, purity, and method of analysis. The fact that an ingredient is listed in any of the U.S.P. publications, including the U.S.P. DI does not mean that your product or another product is necessarily recognized as safe and effective for its intended uses. Further, the U.S.P. DI documents are not "full disclosure" documents that include all the information required by law and regulation.

On September 24, 1998 during a telephone conference call between yourself, this office, and our Raleigh, North Carolina field office, you were asked to identify the location of your remaining product inventory reportedly consisting of approximately

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quinacrine pellets and quinacrine filled inserters. At that time and thus far, you have chosen not to provide us with the location of your products. The FDA is concerned about the health of women and children in the United States and other countries, and that this product may be exported to another country or distributed for use in the United States. We request that you immediately halt all distribution of any and all quinacrine under your control, identify its location, and voluntarily destroy it under FDA supervision.

Your reply to this letter should be addressed to William G. Nychis, Compliance Officer, U.S. Food & Drug Administration, OTC Compliance Team (HFD-312), at the address noted above. You may contact him directly by telephone (301-827-7362) if necessary.

Sincerely,

A handwritten signature in dark ink, appearing to read 'Bradford W. Williams', with a long horizontal flourish extending to the right.

Bradford W. Williams  
Director  
Division of Labeling and  
Nonprescription Drug Compliance  
Center for Drug Evaluation and Research